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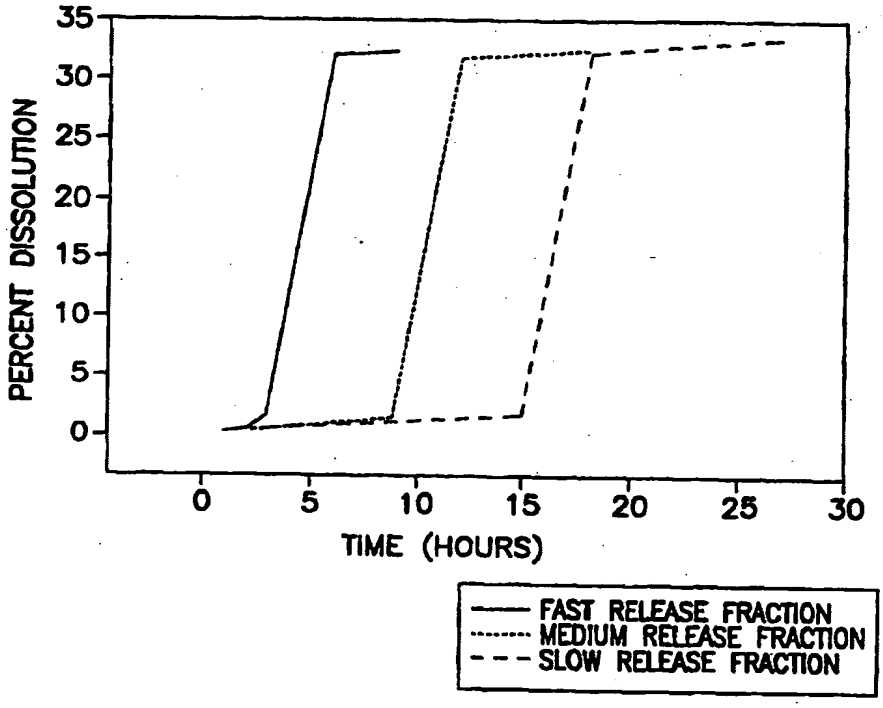
(54) Title: PULSATILE DELIVERY OF DILTIAZEM HCl

(57) Abstract

Controlled and time release of diltiazem-HCl has been of reduced effectiveness because of potential gastrointestinal irritation (based upon materials selected to provide the pulse) or inaccuracy in the timing of the delivery system. The drug delivery system of the present invention delivers diltiazem HCl in a site-specific, time-controlled manner at the gastrointestinal sites, i.e., the duodenum, the ileum, and the colon. In the duodenal site, there is a high rate of absorption and a short residence time (less than one hour). In the duodenal site, there is a high rate of absorption and a short residence time (less than one hour). In the ileal state, there is a medium rate of absorption and a long residence time (about three hours). In the colonic site, there is a low rate of absorption and longer residence time (about 12 hours). Accordingly, the time-controlled delivery of the drug to the duodenal, ileal, and colonic sites achieves a pulsatile release kinetics, particularly where diltiazem (due to intestinal metabolism/first pass effect) is biotransformed faster when the drug is delivered in a pulsatile manner, leading, therefore, to a higher drug concentration in the blood at given dosages.



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PULSATILE DELIVERY OF DILTIAZEM HCl

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to a drug delivery system, and, more particularly, to a pulsatile drug delivery system for diltiazem HCl capable of site-specific delivery and pulsatile (bolus) kinetics.

Description of the Prior Art

Several investigators have developed pulsatile drug delivery systems that provide slow and/or fast release of a drug based upon physical conditions such as pH, temperature, ionic strength, glucose concentration of metabolites (U.S. Patent No. 5,226,902); use expandable core material that can be released at specific sites over a period of time (U.S. Patent No. 4,649,043); or employment of an orificed wall constructed of an elastomer that stretches under pressure as osmotic infusion progresses (U.S. Patent No. 5,221,278).

Publications report the development of programmable pulsatile drug delivery systems from an erodible association of a polymer system and a multi-laminate sample design with alternating drug-loaded layers that deliver a drug only when and where it is needed, at the minimum dose level required to elicit therapeutic results. (Pharmaceutical Research, Vol. 16, No. 8, 1993. "Programmable Drug Delivery from an Erodible Association Polymer System", Xin Xu and Ping I, Lee.) Others report the use of hydrophobic material and surfactant that allows for rapid release after a predetermined lag time. (Journal of Controlled Release, Vol.31 1994, 99-108. "The Time Clock System: a New Oral Dosage Form for Fast and Complete Release of Drug after a Predetermined Time", F. Pozzi, P. Furlani, A. Gazzaniga, S.S. Davis, I.R. Wilding.).

Still others report that, by varying the thickness of the film or coating over the drug, drug release after the lag period can be enhanced by electrostatic or other physiochemical interactions between the polymer and organic acids.

These investigators have included organic acids such as succinic acid into the systems, in order to design a drug delivery system that provides pulsatile kinetics of drug release. (Pharmaceutical Research, Vol. 11, No. 1, 1994, "An Organic Acid-Induced Sigmoidal Release System for Oral Controlled-Release Preparations", S. Narisawa, M. Nagata, C. Danyoshi, H. Yoshino, K. Murata, Y. Hirakawa, and K. Noda.) However, the use of such gastrointestinal-irritants as these acids and the chronic exposure of the gastric mucosa to such irritant materials can create a potential for mucosal damage.

Several patents have been granted with regard to a controlled release diltiazem core. These insolubles include organic acids such as fumaric acid, succinic acid, malic acid and adipic acid, as well as lubricants such as talc, sodium stearate, magnesium stearate, and stearic acid. The presence of the organic acids can have a deleterious effect in the gastrointestinal tract. Additionally, the controlled release formulations of these patents did not permit efficacious drug delivery while providing rate-controlled delivery of drug molecules at the site of absorption in the gastrointestinal (G.I.) tract.

SUMMARY OF THE PRESENT INVENTION

One aspect of the present invention is to provide a process for the pulsatile delivery of diltiazem HCl for drug delivery in a site-specific manner.

Another aspect of the present invention is to produce a pulsatile delivery of diltiazem by having at least three pulses comprising an early duodenal pulse, a medium ileal pulse, and a decayed colonic-specific pulse at time-controlled rates. The individual pulses are provided by distinct particulates which are mixed together.

Another aspect of the present invention is to provide a pulsatile delivery of diltiazem HCl having rapid gastric emptying, regardless of prandial state.

Another aspect of the present invention is to provide a drug delivery system for diltiazem HCl based on gastrointestinal-duodenal transit time, small intestinal transit time, and colonic transit time, for the most effective delivery of diltiazem HCl.

Another aspect of the present invention is to provide enhanced bioavailability of diltiazem HCl in humans through a pulsatile delivery system.

Still another aspect of the present invention is to deliver deltiazem HCl over a 24 hour period with a single dose intake, in a time-dependent, site specific reliable manner.

SUMMARY OF THE INVENTION

These and other aspects of the present invention are achieved by a formulation of three distinct particulate fractions comprising a fast release fraction, a medium release fraction, and a slow release fraction of diltiazem HCl wherein each fraction comprises diltiazem cores layered with polymeric membrane coatings to obtain a fast release fraction having a membrane coating weight gain of 14-18%, a medium release fraction having a membrane coating weight gain of 39-43%, and a slow release fraction having a membrane coating weight gain of 63-67%. These membrane coating weights, dependent upon the materials selcted for the coatings, may vary with other materials to provide release which is time specific with respect to release within an early duodenal pulse, a medium ileal pulse, and a decayed colonic-specific pulse at time-controlled rates. These timed release rates are intended to provide release based on gastrointestinal-duodenal transit time, small intestinal transit time, and colonic transit time, for the most effective delivery of diltiazem HCl.

BRIEF DESCRIPTION OF THE DRAWINGS

These and other aspects of the present invention will be readily appreciated by reference to the following detailed description when taken with the accompanying drawings, wherein like numerals designate like parts throughout, and wherein:

Fig. 1 is a graph of the dissolution profile of each fraction:

Fig. 2 is a graph of the dissolution profile of the formulation of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The drug delivery system of the present invention delivers diltiazem HCl in a site-specific, time-controlled manner at the gastrointestinal sites, i.e., the

duodenum, the ileum, and the colon. In the duodenal site, there is a high rate of absorption and a short residence time (less than one hour). In the duodenal site, there is a high rate of absorption and a short residence time (less than one hour). In the ileal state, there is a medium rate of absorption and a long residence time (about three hours). In the colonic site, there is a low rate of absorption and longer residence time (about 12 hours). Accordingly, the time-controlled delivery of the drug to the duodenal, ileal, and colonic sites achieves a pulsatile release kinetics, particularly where diltiazem (due to intestinal metabolism/first pass effect) is biotransformed faster when the drug is delivered in a pulsatile manner, leading, therefore, to a higher drug concentration in the blood at given dosages.

A fast release fraction of diltiazem HCl is prepared by forming multilayers of a membrane coating dispersion on the drug bead substrate with a weight gain of from 14 to 18%, preferably 15 to 17% and, more particularly, 16%. The membrane coating dispersion is comprised of a water insoluble, slightly permeable, non-enteric polymer compound such as acrylic resins comprising copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium group, sold under the trademark Eudragit RS, described in the brochure of Messrs. Rohm Pharma. GmbH (1985). The Eudragit RS is slightly permeable. In addition to said polymeric compound in the membrane coating dispersion are plasticizers such as triethyl citrate and antiadherents such as silicone dioxide and talc, thoroughly mixed in water.

After multilayering with the membrane coating dispersion, the membrane coated beads are finish-coated with an Opadry/water dispersion (10% w/w). The beads are then dried and subjected to dehydrothermal treatment at from 45 to 50 degrees for 24 hours to complete membrane formation by removing excess moisture.

A medium release fraction of diltiazem HCl is similarly prepared by forming a multilayer of a membrane coating dispersion on the drug bead substrate; however, the weight gain is from 39 to 43%, preferably 40 to 42%

and, more particularly, 41%. The resulting medium release beads are finish coated and likewise subjected to dehydrothermal treatment.

The slow release fraction of diltiazem HCl is also prepared by forming a multilayear membrane coating on the drug bead substrate, but with a weight of from 63 to 67%, preferably 64 to 66%, and more particularly, 65%. The slow release beads are finish coated and subjected to dehydrothermal treatment. The drug release system of the present invention is comprised of fast, medium and slow release fractions in a ratio of 33 1/3: 33 1/3: 33 1/3. Figure 1 illustrates a dissolution profile of each fraction, whereas Figure 2 illustrates the combined dissolution profile. The drug release was determined in a Type 2 dissolution apparatus (paddle), according to U.S. Pharmacopoeia XXIII at 37 degrees in 0.1N HCl.

A drug delivery system for diltiazem•HCl is described which comprises a blend of fast, medium and slow release fractions of a multi-layered diltiazem bead substrate. The fast release fraction comprised of a diltiazem bead substrate is layered with a polymeric membrane coating having a membrane coating weight gain of from 14 to 18 percent. The medium release fraction comprises a diltiazem bead substrate layered with a polymeric membrane coating having a membrane coating weight gain of from 39 to 43 percent. The slow release fraction comprises a diltiazem bead substrate layered with a polymeric membrane coating having a membrane coating weight gain of from 63 to 67 percent. This drug delivery system for diltiazem•HCl preferably has a fast release fraction with a membrane coating weight gain of from 15 to 17 percent, the medium release fraction having a membrane coating weight gain of from 40 to 42 percent and the slow release fraction having a membrane coating weight gain of from 64 to 66 percent by weight. The most preferred drug delivery system for diltiazem•HCl provides a fast release fraction has a membrane coating weight gain of 15-17 percent, and most preferably about 16 percent, the medium release fraction provides a membrane coating weight gain of about 40-42 percent, most preferably about 41 percent by weight, and the slow release fraction has a membrane coating weight gain of about 64-66 percent and most

preferably about 65 percent. Optimal performance of each of said release fractions is where each fraction is dissolved in less than three (3) hours.

The invention also describes a method of treating cardiovascular disorders with a diltiazem•HCl formulation suitable for a once-a-day oral administration comprising administering an effective amount of diltiazem•HCl formulation having a fast release fraction, a medium release fraction and a slow release fraction, the fast release fraction comprised of a multi-layered diltiazem bead substrate layered with a polymeric membrane coating having a membrane coating weight gain of from 14 to 18 percent, the medium release fraction comprised of diltiazem bead substrate layered with a polymeric membrane coating having a membrane coating weight gain of from 39 to 43 percent and the slow release fraction comprised of a diltiazem bead substrate layered with a polymeric membrane coating having a membrane coating weight gain of from 63 to 67 percent.

EXAMPLES OF THE PRESENT INVENTION

The preparation process and resulting product of the present invention are described in the following specific examples, which are intended to be merely illustrative, and the present invention is intended not to be limited thereto.

Example I

Preparation of Drug Bead Substrate

The drug layer dispersion is prepared by weighing purified water into a tared container equipped with air mixer/propeller stirrer. With vigorous mixing, hydroxypropylmethyl cellulose (Opadry Y-5-7095) and diltiazem HCl USP are dispersed in water. The dispersion is mixed for 40 minutes until completely suspended; 30/35 mesh nonpareil seeds (Nu-pareil White) are then dispensed into a poly bag-lined vessel. The seeds are then charged into a Wurster Film coater (GPCG-5 " Wurster HS by Glatt Air Techniques, Ramsey, N.J.).

The fluidization of nonpareils is started at an appropriate volume. The spraying of each drug layer dispersion is started at an appropriate spray rate.

Inlet temperature, air volume, and spray rate are adjusted to layer drug dispersion effectively onto the seeds. When the dispersion is finished, a subcoat is applied. The subcoat is prepared by dispersing hydroxypropylmethyl cellulose (Opadry YS-307065) in purified water. The total layering operation lasts more than four hours. The actual yield of layered beads is 99%; particle size analysis is as follows:

Mesh	14	16	18	20	30	Pan	
Per cent							Total
Retained	1	2	94	3	0	0	100

Example II

Preparation of Fast Release Fraction (FRF)

A fast release fraction having 14 to 18% weight gain on the drug bead substrate is produced by depositing multilayers of a membrane coating dispersion on the drug bead substrate, using a water-insoluble, slightly permeable, non-enteric polymethacrylate compound such as RS (chemically, polyethylacrylate-methyl methacrylate trimethyl ammonium chloride) or poly (EA-MMA-TAMCL, which is available in a 1:2:0.1 ratio.

For preparation of the current invention, an RS 30D Stock Membrane Coating Dispersion is prepared by screening Eudragit RS 30D (30% w/w solids) through a U.S. standard 30 mesh screen into a tared vessel equipped with an air mixer. To the RS 30D is added plasticizer triethyl citrate (TEC) and silicone dioxide (Syloid 244 FP) as an antiadherant, which must be added to prevent agglomeration of RS 30D-coated beads due to significant decrease in the glass transition temperature (T). In another tared container equipped with an air mixer, talc USP is added to purified water. The separately prepared dispersions of RS 30D/TEC/Syloid/water and talc/water are mixed thoroughly.

Next, a division of drug-layered beads and RS 30D (SMCD) is carried out to determine amounts of RS 30D Stock Membrane Coating Dispersion necessary to prepare the FRF and SRF components of the final product.

First, the quantity of layered drug beads (calculated for FRF) is dispensed into the Wurster film coater (GPCG-5 7" Wurster HS by Glatt). Using an appropriate air volume, inlet temperature and spray rate, the designer applies the quantity of RS 30D stock membrane Coating Dispersion until it is depleted, with sufficient purified water sprayed at a reduced rate, to clean the nozzle. The water is sprayed for five minutes while adjusting coating parameters for the subsequent Opadry finish coat. Opadry dispersion (10% w/w) is sprayed onto membrane coated beads at an appropriate spray rate, air volume and inlet temperature. When the opadry finish coat application is completed, the product (FRF) is dried at current parameters for five minutes, and then discharged and reconciled. Actual yield of the membrane-coated beads (FRF) is 99% and particle size analysis is as follows:

Mesh	14	16	18	20	30	Pan	
Per cent							Total
Retained	1	43	55	1	0	0	100

Example III

Preparation of Medium Release Fraction

A quantity of layered drug beads (calculated for MRF) are dispensed into the Wurster film coater (GPCG-5 7" Wurster HS by Glatt). The process employed for preparation of the FRF is repeated for the MRF. Actual yield of the membrane-coated beads (MRF) is 98%; particle size analysis is as follows:

Mesh	14	16	18	20	30	Pan	
Per cent							Total
Retained	1	68	31	1	0	0	100

Example IV

Preparation of Slow Release Fraction (SRF)

A quantity of layered drug beads (calculated for SRF) are dispensed into the Wurster film coater (GPCG-5 7" Wurster HS by Glatt). The process employed for preparation of FRF was repeated for SRF. Actual yield of the membrane-coated beads (SRF) is 98%; particle size analysis is as follows:

Mesh	14	16	18	20	30	Pan	
Per cent							Total
Retained	1	94	5	0	0	0	100

Example V

Dehydrothermal Treatment

The fast, medium and slow release fractions are given dehydrothermal treatment at 45-50 degrees C. For 24 hours in a forced-air oven, to complete the membrane formation process by removing excess moisture.

Example VI

Drug Delivery System

In a triple-filing process, the fast, medium and slow release fractions are filled in the same capsule, in a ratio of 33 1/3, 33/1/3, and 33 1/3. Furthermore, the desirable release profile will be obtained if the weight gain of individual fractions (FRF, MRF and SRF) are controlled within narrow limits, such as 15-17 (FRF), 39-41 (MRF), and 63-65 for SRF.

Example VII

	Mg/capsule	Batch Quantities (20,000 capsules) (kg)	
Diltiazem HCl, USP	300.0		6.0
Nupareil sugar sphere	85.0		1.7
Hydroxypropylmethyl Cellulose	33.71		0.674
	4118.71		8.374
RS 30D (Dry Basis)		3.000	
Triethyl Citrate		0.600	
Talc, USP		0.600	
Syloid 244FP		0.030 4.230	

In order to prepare a batch of 20,000 capsules, a 4% w/w dispersion of hydroxypropylmethyl cellulose (HPMC) was prepared in water using a Lightning Mixer (equipped with an impeller). Then, 6.0 kg of diltiazem hydrochloride was slowly suspended in the HPMC dispersion. The preparation of the dispersions was mixing these ingredients as a controlled RPM.

Then the HPMC/Diltiazem HCl dispersion was pumped through a calibrated, peristaltic pump to deliver the HPMC/Diltiazem dispersion to fluidized Nu-Pareil white core substrate at an appropriate air volume. The HPMC/Diltiazem HCl dispersion was sprayed at an appropriate spray rate. The inlet air temperature, air volume, and spray rate were adjusted to effectively layer the entire HPMC/Diltiazem HCl dispersion on to Nu-Pareil white core substrate. Then, a sub-coat of a proprietary HPMC (Opadry^{R} YS-3 7065) was applied to layered drug beads in order to, theoretically, provide a weight gain of one percent, using fluidized film coating equipment.

A stock dispersion of membrane coat was prepared by plasticizing RS 30D (10 kg of 30% w/w dispersion in water) with 20% of the plasticizer triethyl

citrate (TEC), 20 percent of talc, and 1 percent of Syloid 244 FP, based on the amount of RS 30D on a dry basis. The membrane coat dispersion was applied to provide a 16% (fast release fraction), 39% (medium release fraction), and 63% (slow release fraction) weight gains, respectively, using the fluidized film coating equipment.

Then, a sub-coat of a proprietary HPMC (Opadry^{R} YS-3 7065) was applied to the membrane coated beads in order to, theoretically, provide a weight gain of 2 percent, using fluidized film coating equipment.

What is Claimed:

1. A drug delivery system for diltiazem•HCl, which comprises:

a blend of fast, medium and slow release fractions of a multi-layered diltiazem bead substrate, said fast release fraction comprised of a diltiazem bead substrate layered with a polymeric membrane coating having a membrane coating weight gain of from 14 to 18 percent, said medium release fraction comprised of a diltiazem bead substrate layered with a polymeric membrane coating having a membrane coating weight gain of from 39 to 43 percent and said slow release fraction comprised of diltiazem bead substrate layered with a polymeric membrane coating having a membrane coating weight gain of from 63 to 67 percent.

2. The drug delivery system for diltiazem•HCl as defined in Claim 1, wherein said fast release fraction has a membrane coating weight gain of from 15 to 17 percent, said medium release fraction having a membrane coating weight gain of from 40 to 42 percent and said slow release fraction having a membrane coating weight gain of from 64 to 66 percent.

3. The drug delivery system for diltiazem•HCl as defined in Claim 2, wherein said fast release fraction has a membrane coating weight gain of 16 percent, said medium release fraction having a membrane coating weight gain of 41 percent and said slow release fraction having a membrane coating weight gain of 65 percent.

4. The drug delivery system for diltiazem•HCl as defined in Claim 1 wherein each of said release fraction are dissolved in less than three (3) hours.

5. A method of treating cardiovascular disorders with a diltiazem•HCl formulation suitable for a once-a-day oral administration comprising:

administering an effective amount of diltiazem•HCl formulation having a fast release fraction, a medium release fraction and a slow release fraction, said fast release fraction comprised of a multi-layered diltiazem bead substrate layered with a polymeric membrane coating having a membrane coating weight gain of from 14 to 18 percent, said medium release fraction comprised of diltiazem bead substrate layered with a polymeric membrane coating having a membrane coating weight gain of from 39 to 43 percent and said slow release fraction comprised of a diltiazem bead substrate layered with a polymeric membrane coating having a membrane coating weight gain of from 63 to 67 percent.

6. The method of treating cardiovascular disorders as defined in Claim 5 wherein said fast release fraction has a membrane coating weight gain of from 15 to 17 percent, said medium release fraction having a membrane coating weight gain of from 40 to 42 percent and said slow release fraction having a membrane coating weight gain of from 64 to 66 percent.

7. The method of treating cardiovascular disorders as defined in Claim 6 wherein said fast release fraction has a membrane coating weight gain of 16 percent, said medium release fraction having a membrane coating weight gain of 41 percent and said slow release fraction having a membrane coating weight gain of 65 percent.

8. The method of treating cardiovascular disorders as defined in Claim 5 wherein said diltiazem•HCl formulation exhibits the following in-vitro dissolution pattern when measured in a type 2 dissolution apparatus, according to US Pharmacopia XXIL, in 0.1N HCl at 100 rpms;

(a) from zero to 33 percent of total diltiazem is released after six (6) hours of measurement in said apparatus;

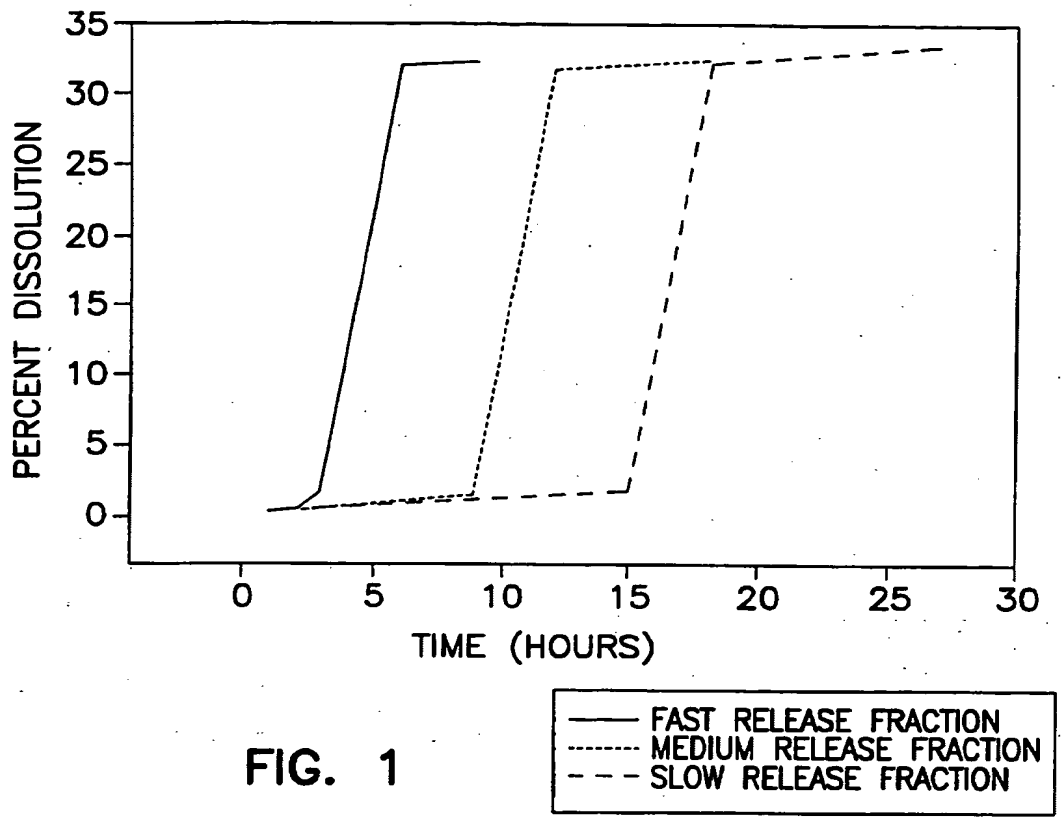
(b) from 33 to 66 percent of total diltiazem is released after twelve (12) hours of measurement in said apparatus; and

(c) from 66 to 100 percent is released after eighteen (18) hours of measurement in said apparatus.

9. A drug delivery system for diltiazem•HCl, which comprises:

a blend of fast, medium and slow release fractions of a multi-layered diltiazem bead substrate, said fast release fraction comprised of a diltiazem bead substrate layered with a polymeric membrane coating having a membrane coating weight gain which provides a pharmacologicallly effective rate of release into the duodenal region of the human gastrointestinal tract within one hour, said medium release fraction comprised of a diltiazem bead substrate layered with a polymeric membrane coating which provides a pharmacologicallly effective rate of release into the ileal site of the gastrointestinal tract of a human within about one to three hours, and said slow release fraction comprised of diltiazem bead substrate layered with a polymeric membrane coating having a membrane coating which provides a pharmacologicallly effective rate of release into the colonic site of the gastrointestinal tract of a human within about three to twelve hours.

10. The drug delivery system of claim 9 wherein said fast release fraction comprises a multi-layered diltiazem bead substrate layered with a polymeric membrane coating having a membrane coating weight gain of from 14 to 18 percent, said medium release fraction comprises a diltiazem bead substrate layered with a polymeric membrane coating having a membrane coating weight gain of from 39 to 43 percent and said slow release fraction comprises a diltiazem bead substrate layered with a polymeric membrane coating having a membrane coating weight gain of from 63 to 67 percent.


PERCENT DISSOLUTION
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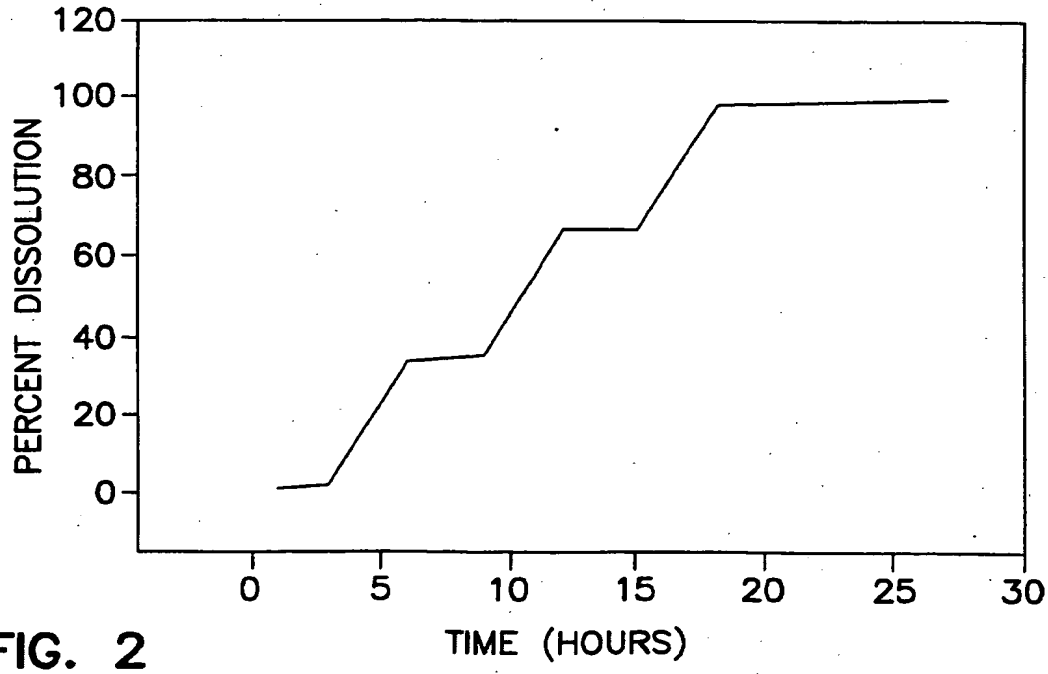
30
25
20
15
10
5
0
0
5
10
15
20
25
30
TIME (HOURS)
FAST RELEASE FRACTION
MEDIUM RELEASE FRACTION
SLOW RELEASE FRACTION

FIG. 1


PERCENT DISSOLUTION
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100
80
60
40
20
0
0
5
10
15
20
25
30
TIME (HOURS)

FIG. 2

INTERNATIONAL SEARCH REPORT

Inte. .tional application No.
PCT/US 98/01063

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/26, A61K 9/54, A61K 31/55
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

USPAT FULL, WPI, CAPLUS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9428882 A1 (CHEN, CHIH-MING), 22 December 1994 (22.12.94), page 2, line 28 - page 3, line 14; page 7, line 9 - line 14, claims 4,7	1-10
X	US 5229131 A (GORDON L. AMIDON ET AL), 20 July 1993 (20.07.93), column 2, line 48 - line 57; column 6, line 59 - column 7, line 6	1-10
X	EP 0527637 A1 (EUROCELTIQUE SA), 17 February 1993 (17.02.93), page 2, line 42 - page 3, line 8, claim claims	1-10

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 May 1998	03 07 1998
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Authorized officer Anneli Jönsson

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/01063

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0324981 A1 (ALFA WASSERMANN S.P.A.), 26 July 1989 (26.07.89) -- --------	1-10

INTERNATIONAL SEARCH REPORT

In ational application No.
PCT/US 98/01063

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 5-8
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

SA 84702

INTERNATIONAL SEARCH REPORT

Information on patent family members

29/04/98

International application No.
PCT/US 98/01063

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